REMARKS

Claims 1-3, 5, 6, 11-13, 23-26, and 42-56 constitute the pending claims in the present application, prior to Amendment. Applicants cancel, without prejudice, claims 42-48. Applicants reserve the right to prosecute claims of similar or differing scope in this or future applications.

Applicants have amended claims 1, 2, 23, 49, 52, and claims dependent thereon, to more particularly point out certain embodiments of Applicants' invention. Claim 1 has been amended to more particularly point out that the neuronal cell is a "dopaminergic" neuronal cell. Support for Applicants' amendment can be found, for example, in paragraph [0040] and Example 10 of the published specification. Claim 1 has also been amended to more particularly point out the Sonic hedgehog polypeptides for use in the claimed method based on both structural and functional characteristics. Support for Applicants' amendment can be found, for example, in paragraphs [0022], [0065], [0066], [0096], and Table 1 of the published specification.

Claim 2 has been amended to more particularly point out that the neuronal cell is a "dopaminergic neuron or a motor neuron". Support for Applicants' amendment can be found, for example, in paragraph [0040] and Examples 9-10 of the published specification. Claim 1 has also been amended to more particularly point out the Sonic hedgehog polypeptides for use in the claimed method based on both structural and functional characteristics. Support for Applicants' amendment can be found, for example, in paragraphs [0022], [0065], [0066], [0096], and Table 1 of the published specification.

Claim 23 has been amended to more particularly point out that the neuronal cell type to which the cell is induced to differentiate is a dopaminergic neuron or motor neuron. Support for Applicants' amendment can be found, for example, in paragraph [0040] and Examples 9-10 of the published specification. Claim 23 has also been amended to more particularly point out the Sonic hedgehog polypeptides for use in the claimed method based on both structural and functional characteristics. Support for Applicants' amendment can be found, for example, in paragraphs [0022], [0065], [0066], [0096], and Table 1 of the published specification.

Claim 49 has been amended to more particularly point out that the neuronal cell type to which the cell is induced to differentiate is a dopaminergic neuron or motor neuron. Support for Applicants' amendment can be found, for example, in paragraph [0040] and Examples 9-10 of the published specification. Claim 49 has also been amended to more particularly point out the

Sonic hedgehog polypeptides for use in the claimed method based on both structural and functional characteristics. Support for Applicants' amendment can be found, for example, in paragraphs [0022], [0065], [0066], [0096], [0112], [0113], and Table 1 of the published specification.

Claim 52 has been amended to more particularly point out the Sonic hedgehog polypeptides for use in the claimed method based on both structural and functional characteristics. Support for Applicants' amendment can be found, for example, in paragraphs [0022], [0065], [0066], [0096], [0112], [0113], and Table 1 of the published specification.

Applicants add new claims 57-81. Support for the subject matter of the newly added claims is found throughout the specification. No new matter has been entered. Specifically, claims 57-65 are dependent claims that more particularly point out elements recited in preceding base claims. Claims 66-81 are means-plus-function claims based on the pending independent claims and in compliance with 35 U.S.C. § 112, sixth paragraph.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Rejection of Claims 1-3, 23, 25, 26, 29, and 36-41 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 23, 25, 26, 29, and 36-41 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

The Examiner states that use of the term "hedgehog polypeptide" without reference to specific amino acid sequences is indefinite because the specification "does not identify that material element or combination of elements which is unique to, and therefore, definitive of 'hedgehog polypeptide[s]'." Applicants respectfully disagree with the Examiner's characterization of the teachings of the specification. The specification teaches both structural and functional features of hedgehog polypeptides, and provides multiple hedgehog family members from numerous evolutionarily distinct species (e.g., fish, chick, mouse, human). As such, one of skill in the art can readily ascertain the metes and bounds of a claim directed to the use of a Sonic hedgehog polypeptide.

Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out the claimed subject matter. Specifically, Applicants have amended the claims to refer to the Sonic hedgehog polypeptides for use in the claimed methods with reference to structural features (e.g., amino acid sequence and molecular weight), as well as functional features (e.g., the polypeptide binds a hedgehog receptor and promotes hedgehog signaling). As such, one of skill in the art can readily envision the polypeptides for use in the claimed methods.

The Examiner also states that recitation of a "bioactive" fragment of a hedgehog polypeptide renders the claims indefinite. Once again, Applicants respectfully disagree. Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out the fragments for use in the claimed methods. Specifically, the fragments are described with reference to their sequence, molecular weight, and functional characteristic of binding a hedgehog receptor and promoting hedgehog signaling. As such, one of skill in the art can readily ascertain the claimed subject matter.

Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Applicants' amendments are believed to obviate the rejection, and reconsideration and withdrawal of this rejection are requested.

Rejection of Claims 1-3, 5, 6, 11-13, 23-26, and 42-56 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 5, 6, 11-13, 23-26, and 42-56 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the enablement requirement. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

The Examiner states that while the specification is enabling for methods of promoting growth, differentiation and/or survival of embryonic neural cells by administering a Sonic hedgehog polypeptide of SEQ ID NOs: 8, 11, 12 or 13 or an N-terminal auto-proteolytic portion thereof, it does not enable use of a polypeptide other than one of SEQ ID NOs: 8, 11, 12 or 13 or other than N-terminal auto-proteolytic portions thereof. The Examiner further states that the specification is not enabling for promoting growth, differentiation and/or survival of neuronal cells other than embryonic cells. The Examiner then makes several assertions as alleged support for the rejection, and references certain papers published after the filing of the instant application that allegedly support the rejection. Applicants will address the Examiner's position below.

The Examiner maintains that, since the specification disclosed experiments that indicated that Sonic hedgehog was not expressed in adult tissues, one of skill in the art would not expect that adult tissues would be responsive to hedgehog. However the subjective beliefs of others in the field is not the relevant question when assessing enablement of the claimed invention. Rather, the question is whether one of skill in the art could practice the claimed invention based on the specification and the level of skill in the art. In the present case, the answer is a resounding "yes" - supported by extensive post filing evidence demonstrating the efficacy of Sonic hedgehog in influencing adult cells, including adult neuronal cells.

In response to the extensive post-filing evidence supporting the claimed invention, the Examiner cited Traiffort et al., 1998 and Miao et al., 1997. The Examiner argued that these references indicate that extensive trial-and-error experimentation is required to practice the claimed invention.

As a first point, Applicants disagree with the Examiner's interpretation of these references. By citing a single sentence from Traiffort, the Examiner minimizes the ways in which the reference supports the claimed invention.

> In developing brain, Shh has the capacity to induce the differentiation of dopaminergic neurons in the midbrain (Hynes et al., 1995; Wang et al., 1995) and motor neurons in the spinal cord (Roelink et al., 1994; Ericson et al., 1997), to promote survival of GABA-immunoreactive neurons and of dopaminergic neurons in culture, and also to prevent dopaminergic neuron death induced by the neurotoxin 1-methyl-4-phenylpyridinium (MPP+) (Miao et al., 1997). Together with the existence of Shh mRNA-expressing cells in restricted regions of the rat brain and the presence of Ptc and Smo mRNA-expressing cells in discrete brain regions, these observations suggest novel prominent roles for Shh in brain signaling with potential therapeutic implications, particularly in neurodegenerative disease. page 1330, column 1,

Applicants contend that Traiffort, taken as a whole, supports the enablement of the claimed invention and summarizes extensive post-filing evidence that supports Applicants' position. Even if Traiffort does review experiments indicating differences amongst neuronal cell types with respect to hedgehog responsiveness, that does not indicate that the level of experimentation required to practice the claimed invention is undue.

The Examiner similarly cites Miao as providing evidence that different cells respond differently to hedgehog signaling. As a first point, it is noted that Miao was offered to demonstrate differences between the responsiveness of embryonic cells and adult cells.

However, Miao does not provide experiments using adult tissues. Rather, Miao provides experiments using older embryonic tissue (E 14.5) taken at a stage following initial specification of certain neuronal cell types. Thus, regardless of whether Miao teaches differences in responsiveness to hedgehog, Miao does not undermine the enablement of the claimed invention with respect to modulating adult cells.

Furthermore, Miao supports Applicants' contention that Sonic hedgehog promotes proliferation, differentiation, and survival of a variety of neuronal cell types. Particular in vitro and in vivo models, such as the embryo explant culture used in Miao, can readily be used by skilled practitioners to practice the claimed invention with respect to a particular cell type or developmental stage. Miao does not reveal that such standard experimentation by skilled practitioners is undue.

Applicants contend that the post-filing evidence of record submitted by Applicants, as well as the very articles cited by the Examiner, support the conclusion that the claims are enabled throughout their scope. The overwhelming weight of the evidence shows that Sonic hedgehog polypeptides modulate proliferation, differentiation, and survival of a wide range of embryonic and adult cell types, as described in the specification. Further, the specification and the state of the art reveal that skilled practitioners can readily test Sonic hedgehog polypeptides in a diverse array of in vitro or in vivo model systems. As such, one of skill in the art can readily practice the claimed invention without undue experimentation.

Applicants previously submitted affidavits and examples of post-filing evidence that support the enablement of the claimed invention. Applicants additionally enclosed herewith an article entitled "Sonic the Hedgehog and the Fate of Neural Stem Cells." This article summarizes the results of primary papers describing the proliferation promoting affects of Sonic hedgehog on adult neural stem cells. (Exhibit 1). This article provides just one more example indicating the successful practice of the teachings of the specification.

Applicants contend that the specification is broadly enabling for methods of promoting proliferation, differentiation, and/or survival of any neuronal cell type. The overwhelming weight of the evidence supports Applicants' position. Nevertheless, to expedite prosecution, Applicants have amended claims 1, 2, 23, 49, and claims dependent thereon, to more particularly point out the neuronal cell types within the scope of the claimed methods. Specifically, the claims have been amended to refer to dopaminergic neurons and/or motor neurons. Applicants'

amendment is not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Applicants' amendments are believed to obviate the rejection, and reconsideration and withdrawal of the rejection is requested.

The rejection is also based on the number of polypeptides that allegedly fall within the scope of the claims. Specifically, the Examiner alleges that one of skill in the art would need to conduct undue experimentation to make and test variants and fragments of Sonic hedgehog to identify functional variants and fragments that can be used in the claimed methods. Applicants respectfully disagree.

As a first point, Applicants note that one of skill in the art is provided with extensive guidance in the making and testing of variant sequences and fragments that can be used to practice the claimed invention. The specification provides numerous hedgehog family members isolated from evolutionarily distinct organisms, thus providing extensive information concerning the structure and function of various portions of the polypeptide. Additionally, the specification teaches that the N-terminal fragment of approximately 19 kDa contains much of the functional activity of the polypeptide. As such, one of skill in the art has extensive guidance for the making and testing of other variants and fragments, as well as controls to assess whether a particular variant or fragment retains the activity (e.g., receptor binding and/or signaling) of a native hedgehog polypeptide.

The Examiner cited references indicating the interrelationship between protein sequence and structure, and thus argues that one cannot predict whether a particular change in sequence will abrogate the function of the protein. In making this assertion, the Examiner implies that mere predictability is the touch stone for assessing enablement. However, predictability is but one factor to consider when assessing enablement. It is not required that the invention be restricted in scope to absolute black-and-white predictability. The test of enablement is whether one of skill in the art could practice the invention throughout its scope without undue experimentation; predictability and foreseeability are relevant only to the extent that undue experimentation is necessary to practice the full scope of the pending claims.

With regard to the making and testing of variant sequences and fragments, the technology available at the time of filing permitted the preparation and testing of vast numbers of variant sequences with little or no human intervention whatsoever – the very essence of "routine experimentation." Such sequences could then be readily tested in any conventional in vitro or in

vivo assay to readily identify sequences that retained one or more of the functional characteristics of the native polypeptide.

The instant specification itself discusses in great detail techniques for making and testing variant sequences. For example, the specification discusses combinatorial mutagenesis at great length, and such techniques were highly developed in the art by the time the present application was filed. See, for example, paragraphs [0100], [0137], [0158], [0165], and [0171]-[0172] of the published specification. Further, the specification provides numerous examples of assays that could be used to evaluate whether a particular variant or fragment retained the activity of a native Sonic hedgehog polypeptide. See, for example, paragraphs [0166], [0167], and [0196] of the published specification.

In addition, Applicants provide herewith as Exhibit **2** copies of Gallop et al., *J. Med. Chem.* **1994**, *37,* 1233-1251; Graham et al. *Biochemistry* **1993**, *32*, 6250-6258; Chan et al. *J. Bacteriol.* **1993**, *175*, 858-865; Osuna et al. *Gene* **1991**, *106*, 7-12; York et al., *J. Biol. Chem.* **1991**, *266*, 8495-8500; Sandberg et al. *Proc. Natl. Acad. Sci.* **1993**, *90*, 8367-8371; Wissmann et al. *Genetics* **1991**, *128*, 225-232; Delagrave et al., *Protein Engineering* **1993**, *6*, 327-331; and Reidhaar-Olson et al., *Science* **1988**, *241*, 53-57, all of which were published well in advance of the filing of the present application and support Applicants' contention that the use of combinatorial mutagenesis to generate active variant sequences for a known sequence was readily practiced. As such, generating and testing a large number of variant sequences and fragments does not constitute undue experimentation, irrespective of whether one can predict which variants will retain activity. Applicants point out in particular Reidhaar-Olson et al. and Delagrave et al. as describing especially powerful techniques for generating variant sequences.

In evaluating the enablement of the claimed subject matter, both the courts and the MPEP have acknowledged that some experimentation is permissible, as long as that experimentation is not undue (MPEP 2164.04). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). However, the courts have been clear that the determination of whether undue experimentation is required should not be made based solely on the time and cost involved in conducting such experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction

in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). "Time and expense are merely factors in this consideration and are not the controlling factors." *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

Applicants contend that in view of the guidance provided in the specification and the level of skill in the art regarding the making and testing of variant sequences, one of skill in the art could readily make and test a wide range of Sonic hedgehog fragments and variants without undue experimentation. Further, one of skill in the art could readily test the variants and fragments to identify polypeptides for use in the claimed methods (e.g., polypeptides that bind a hedgehog receptor and promote hedgehog signaling). As such, the practice of the full scope of the claimed invention does not involve undue experimentation.

Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out certain embodiments of the claimed invention. Specifically, Applicants have amended claims 1, 2, 23, 49, 52, and claims dependent thereon, to more particularly point out the hedgehog polypeptides for use in the claimed methods. As amended, the claims are directed to the use of Sonic hedgehog polypeptides specified according to both structural characteristics (sequence and molecular weight) and functional characteristics (ability to bind the hedgehog receptor and promote hedgehog signaling).

Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Applicants' amendments are believed to obviate the rejection, and reconsideration and withdrawal of this rejection are requested.

Applicants maintain the arguments of record. The specification explicitly contemplates that hedgehog polypeptides can be used to influence not only the behavior of embryonic cells and tissues, but also the behavior of adult cells. In further support of the methods explicitly taught by the application, Applicants have cited post-filing evidence demonstrating that, as taught by the application as filed, hedgehog polypeptides can be used to influence the proliferation, differentiation and survival of adult cells including neuronal cells and stem cells. Applicants contend that the wealth of post-filing evidence supports the enablement of the claimed subject matter. Simply put, Applicants taught that hedgehog polypeptides **could** be used to influence the behavior of adult cells including neuronal cells, and hedgehog polypeptides **can** in fact be used to influence the behavior of adult cells including neuronal cells. In light of the

extensive guidance provided by the specification and the overwhelming evidence in the literature, Applicants maintain that there is no reasonable basis to question the enablement of the claimed subject matter. One of skill in the art can readily practice the claimed invention generally, or with respect to particular cell types and developmental stages, without undue experimentation.

The Examiner appears to equate the instant disclosure with the "mere germ of an idea." Applicants respectfully disagree. As indicated by the paragraphs referenced above, the specification specifically discusses the use of hedgehog polypeptides to promote proliferation, differentiation, and survival of neuronal tissue. Further, the specification discusses neuronal conditions that can be treated using the claimed polypeptides. Finally, the specification provides working examples indicating that hedgehog polypeptides do in fact influence dopaminergic and motor neurons in embryonic tissue. Applicants fail to see how working examples of efficacy in particular neuronal cell types, and a detailed discussion of various uses in adult tissue, can be construed as the "mere germ of an idea."

In evaluating the enablement of the claimed subject matter, both the courts and the MPEP have acknowledged that some experimentation is permissible, as long as that experimentation is not undue (MPEP 2164.04). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). However, the courts have been clear that the determination of whether undue experimentation is required should not be made based solely on the time and cost involved in conducting such experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). "Time and expense are merely factors in this consideration and are not the controlling factors." *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

In the present case, Applicants note that work published within just 1-3 years of Applicants' effective filing date support the claimed invention. Clearly, the tools available to skilled artisans permitted the practice of the claimed invention without undue experimentation.

MPEP 2164.04 outlines the criteria for evaluating enablement. "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

The reasoning outlined in MPEP 2164.04 is well supported by case law stating that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

Furthermore, as exemplified by *In re Strahilevitz*, a broadly enabling disclosure need not include a single working example (*In re Strahilevitz*, 668 F.2d 1229, 212 USPQ 561 (CCPA 1982)). In *Strahilevitz*, the court reversed the Appeal Board's holding of non-enablement, and pointed out that the provisions of 35 U.S.C. 112, first paragraph, do not require that Applicants provide working examples. This sentiment was echoed in *In re Wright* which held that to comply with 35 U.S.C. 112, first paragraph, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."

Finally, both the courts and the Board of Patent Appeals and Interferences have issued opinions which recognize that common sense and prosecutorial expediency contradict decisions that would require Applicants to disclose every last detail of an invention. "Not every last detail [of an invention need] be described [in a patent specification], else patent specifications would turn into production specifications, which they were never intended to be." (*In re Gay*, 390 F.2d 769, 774, 135 USPQ 311, 316 (CCPA 1962)). These sentiments were reiterated by the Board in their decision in *Staehelin v Secher*. Citing *In re Gay*, the Board concluded that "the law does

not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. 112, first paragraph." (*Staehelin v Secher*, 24 USPQ 2d 1513, 1516 (Bd. Pat. App. & Int. 1992).

Applicants contend that the maintenance of this rejection is contrary to the standards for evaluating enablement outlined in the MPEP, and upheld by the Federal Circuit and the Board of Patent Appeals and Interferences. For example, despite the guidance provided by the holdings in *In re Marzocchi*, Applicants have gone through the trouble and expense of making of record an extensive array of post-filing evidence which further supports the enablement of the presently claimed methods. This post-filing evidence includes the declarations of Hank Dudek and Lee Rubin, as well as more than a dozen references from the scientific literature that support Applicants' contention that hedgehog polypeptides can be used to influence the proliferation, differentiation, and survival of a number of embryonic **and** adult cell types.

In maintaining the rejection in the face of this substantial post-filing evidence, the Examiner appears to be requiring Applicants to satisfy not merely the standards for enabling the claimed invention, but rather some sort of super-enablement standard that would have required that Applicants provided working examples, in the specification as filed, demonstrating methods of using hedgehog polypeptides in adult neuronal tissue. Clearly, the courts have balked at the notion that Applicants' claims must be limited in scope to only that which is encompassed by the working examples in the specification. Additionally, the very fact that the post-filing evidence supports the prophetic examples disclosed in the specification argues **strongly** against the appropriateness of applying a higher standard than that used in evaluating enablement in cases such as *In re Gay* and *Staehelin v Secher*.

In response to Applicants' arguments of record, the Examiner raises several counter-arguments. Regarding the issue of whether the claims are enabled for methods of promoting growth, differentiation or survival of both embryonic and adult cells, the Examiner has cited a few references in which a hedgehog polypeptide did not influence the fate of a particular neuronal cell type, and has alleged that these examples demonstrate that one of skill in the art must undergo extensive experimentation in order to practice the claimed invention. Once again, Applicants contend that rejecting the claims simply because the Examiner can find particular examples in which Sonic hedgehog polypeptides do not function to promote growth,

differentiation, or survival is akin to requiring that Applicants satisfy a standard above and beyond that which is required by the MPEP or under the law.

In accordance with MPEP 2164.05, when making a determination as to the enablement provided for the claimed invention, the evidence must be considered as a whole. Furthermore, "the evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP 2164.05). Applicants contend that this burden has been satisfied.

Furthermore, Applicants point out that even if the claims encompass certain inoperative embodiments, that does not undermine the enablement of the operative subject matter. In accordance with MPEP 2164.08(b), "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." This standard has been upheld in the courts, and permits a claim to encompass a finite number of inoperable embodiments so long as inoperable embodiments can be determined using methodology specified in the application without undue experimentation. See, for instance, *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976).

An additional argument raised by the Examiner concerns whether the claims are enabled for the use of polypeptides comprising variant sequences. However, as indicated above, the making and testing of variant sequences is routine and readily practiced without undue experimentation.

Given that the presently claimed methods were explicitly contemplated by the specification as filed, and given that the effective use of these methods has been borne out by the preponderance of the evidence in the field since the filing of this application, Applicants contend that the claims are enabled throughout their scope.

Applicants maintain that the specification is broadly enabling for methods of influencing embryonic and adult cell fate using hedgehog polypeptides. Applicants further maintain that the specification is broadly enabling for methods using hedgehog polypeptides comprising naturally occurring, as well as variant amino acid sequences. The application explicitly contemplates these methods, and a wealth of post-filing evidence has demonstrated that, as taught in the specification, hedgehog polypeptides influence the growth, differentiation, and survival of

embryonic and adult cells. The remaining issues in this case can be summarized with a quotation from *In re Hogan* (*In re Hogan*, 559 F.2d 595, 605-606, 194 USPQ 527, 537 (CCPA 1977)).

> Rejections under 112, first paragraph, on the ground that the scope of enablement is not commensurate with the scope of the claims, orbit about the more fundamental question: To what scope of protection is the applicant's particular contribution to the art entitled?

Applicants contend that the answer to this question is clear. The discovery of vertebrate hedgehog polypeptides and their function in regulating growth, differentiation, and survival of a large number of cell types derived from all three germ layers was a ground-breaking discovery in the fields of cell and developmental biology. That Applicants' prophetic disclosure of the potential roles and uses of hedgehog polypeptides in adult organisms, supported by Applicants' careful analysis of the role of hedgehog during embryonic development, has in fact been subsequently confirmed throughout the scientific and patent literature only serves to further underscore the importance of this invention and of Applicants' broadly enabling disclosure.

Applicants contend that the claims are enabled throughout their scope. Applicants provided a broad disclosure supported by extensive experimentation in embryonic systems, as well as extensive prophetic discussion and direction concerning methods of using hedgehog polypeptides to influence the growth, differentiation, and survival of adult tissues. Applicants respectfully submit that the maintenance of this rejection, and the maintenance of arguments that deprive Applicants' claims of any reasonable breadth, is fundamentally unfair. By attempting to limit Applicants to claims directed to methods of using only polypeptides comprising amino acid sequences identical to naturally occurring Sonic hedgehog, as well as claims directed to methods of using these polypeptides only in embryonic cells, Applicants' participation in the patent process is rewarded with claims that offer virtually no meaningful protection. Applicants cannot believe that such protection is the appropriate outcome for this fundamental and critically important scientific advance.

Nevertheless, to expedite prosecution, Applicants have amended the claims to more explicitly point out specific embodiments of the invention. Applicants have amended claim 1 (and claims dependent thereon) to more particularly point out that the neuronal cell modulated by the claimed Sonic hedgehog polypeptides is a dopaminergic neuronal cell, and to more particularly point out the structural and functional features of Sonic hedgehog polypeptides for

use in the claimed methods. Applicants have amended claim 2 (and claims dependent thereon) to more particularly point out that the neuronal cell responsive to hedgehog induction is a dopaminergic neuron or a motor neuron, and to more particularly point out the structural and functional features of Sonic hedgehog polypeptides for use in the claimed methods. Applicants have amended claims 23 and 49 (and claims dependent thereon) to more particularly point out that the claimed method induced a cell to differentiate to a dopaminergic neuron or a motor neuron, and to more particularly point out the structural and functional features of Sonic hedgehog polypeptides for use in the claimed methods. Applicants have amended claim 52 (and claims dependent thereon) to more particularly point out the structural and functional features of Sonic hedgehog polypeptides for use in the claimed methods.

Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Applicant' amendments are believed to obviate the rejection, and reconsideration and withdrawal of this rejection are requested.

Applicants note that new claims 66-81 are means-plus-function claims in compliance with 35 U.S.C. § 112, sixth paragraph. Applicants contend that the means-plus-function claims are fully compliant with the enablement requirement. Consideration of the newly added claims is requested.

Rejection of Claims 1-3, 5, 6, 11-13, 23-26, 42-56 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 5, 6, 11-13, 23-26, and 42-56 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

The Examiner states that there is no description of methods of promoting growth, differentiation or survival of adult neural cells. The Examiner further states that the description regarding hedgehog protein's effects on embryonic tissues does not support the claimed genera of methods.

Applicants respectfully disagree with the Examiner's characterizations. In evaluating whether the specification demonstrates that Applicants were in possession of the claimed invention, the Examiner is applying case law relevant to written description of compositions, not methods. Such case law is not relevant to the instant application where methods and not compositions are being claimed.

The specification explicitly describes the use of hedgehog polypeptides to promote proliferation, differentiation, and/or survival of a range of embryonic and adult neuronal cell types. See, for example, paragraphs [0040], [0101], [0212] of the published specification. Exemplary cell types include, but are not limited to, dopaminergic neurons and motor neurons. *Id.* Furthermore, the specification discusses numerous diseases and conditions of adult neuronal tissues, and describes how hedgehog polypeptides could be used to treat these conditions. See, for example, paragraphs [0212]-[0217] of the published specification.

Additionally, although the courts have never required that reduction to practice of methods require an actual working example, the specification does provide working examples demonstrating the efficacy of hedgehog polypeptides in modulating cell behavior in embryonic cells, including neuronal cells. See, Examples 9-10.

Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out certain aspects of the claimed invention. Specifically, Applicants have amended claim 1 (and claims dependent thereon) to more particularly point out that the neuronal cell modulated by the claimed Sonic hedgehog polypeptides is a dopaminergic neuronal cell, and to more particularly point out the structural and functional features of Sonic hedgehog polypeptides for use in the claimed methods. Applicants have amended claim 2 (and claims dependent thereon) to more particularly point out that the neuronal cell responsive to hedgehog induction is a dopaminergic neuron or a motor neuron, and to more particularly point out the structural and functional features of Sonic hedgehog polypeptides for use in the claimed methods. Applicants have amended claims 23 and 49 (and claims dependent thereon) to more particularly point out that the claimed methods induce a cell to differentiate to a dopaminergic neuron or a motor neuron, and to more particularly point out the structural and functional features of Sonic hedgehog polypeptides for use in the claimed methods. Applicants have amended claim 52 (and claims dependent thereon) to more particularly point out the structural and functional features of Sonic hedgehog polypeptides for use in the claimed methods.

Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Applicant' amendments are believed to obviate the rejection. Reconsideration and withdrawal of this rejection are requested.

Applicants note that new claims 66-81 are means-plus-function claims in compliance with 35 U.S.C. § 112, sixth paragraph. The newly added claims have not yet been examined,

and thus have not been rejected on any grounds. Nevertheless, Applicants take a moment to note that it is difficult to imagine the circumstances under which a means-plus-function claim could be rejected as lacking sufficient written description. As is clear from the very language of the statute, claims interpreted under 35 U.S.C. § 112, sixth paragraph, are construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof. Thus, the claims are so intimately tied to the disclosure of the specification – for the specification lays the foundation for the scope of the claim in an intimate and inextricable manner – that the claims by definition must be adequately described.

If an Examiner were to base a rejection on the equivalents that fall within the scope of a claim, Applicants would direct the Examiner's attention to MPEP 2182: "The specification need not describe the equivalents of the structures, material, or acts corresponding to the means- (or step-) plus-function claims. See *In re Noll*, 545 F.2d 141, 149-50, 191 USPQ 721, 727 (CCPA 1976) ('The meaning of "equivalents" is well understood in patent law, ... and an applicant need not describe in the specification the full range of equivalents of his invention.' (citation omitted)."

Applicants contend that the pending claims satisfy the written description requirement. Accordingly, reconsideration and withdrawal of this rejection are requested.

Supplemental Information Disclosure Statement

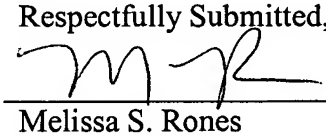
Applicants enclose herewith a Supplemental Information Disclosure Statement to make of record related co-pending applications and issued patents.

Applicants additionally bring to the Examiner's attention commonly owned application serial numbers 08/462,386 and 08/954,771, both of which are abandoned.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. HMSU-P17-006.**

Respectfully Submitted,



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